

### Examiner's Amendment

An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment was given in a telephone interview with Lewis Kreisler on March 3, 2010.

Claim 1 is amended as follows:

1. (Currently amended) A method for treating toxicity due to a pyrimidine nucleoside analog in an animal comprising

administering to ~~an~~ said animal a pharmaceutically effective amount of an acylated derivative of uridine selected from the group consisting of triacetyluridine and ethoxycarbonyluridine or triacetylcytidine,

wherein said pyrimidine nucleoside analog is selected from the group consisting of 5-fluorouracil (5-FU), Tegafur, 5-fluoroorotate, 5'-deoxy-5- fluorouridine, 5-fluorouridine, 2'-deoxy-5-fluorouridine, fluorocytosine, trifluoromethyl-2 '-deoxyuridine, arabinosyl cytosine, cyclocytidine, 5-aza-2'- deoxycytidine, arabinosyl 5-azacytosine, 6-azacytidine, N-phosphonoacetyl-L- aspartic acid (PALA), pyrazofurin, 6-azauridine, azaribine, thymidine, 3- deazauridine, AZT, dideoxycytidine, 5-ethyl-2'-deoxyuridine, 5-iodo-2 ' deoxyuridine, 5-bromo-2 '-deoxyuridine, 5- methylamino-2 '-deoxyuridine,

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arabinosyluracil, dideoxyuridine and (S)-1-(3-hydroxy-2- phosphonylmethoxypropyl)  
cytosine;

and wherein said toxicity is selected from the group consisting of damage to  
hematopoietic tissue and damage to mucosal tissues.

### Detailed Action

This office action is a response to applicant's communication submitted December 4, 2009 wherein claims 1, 20, and 24 are amended and new claims 26-28 are introduced. This application is a divisional application of US application 08/176485, now US patent 5736531, filed December 30, 1993, which is a continuation in part of US application 08/061381, now abandoned, filed May 15, 1993, which is a continuation in part of US application 07/903107, filed June 25, 1992, now abandoned, which is a continuation in part of US application 07/724340, now abandoned, filed July 5, 1991, which is a continuation in part of US applications 07/438493, now abandoned, filed June 26, 1990, and 07/487984, now abandoned, filed February 5, 1990, both of which are continuations in part of US applications 07/115929 and 07/115923 respectively, now abandoned, both filed October 28, 1987.

Claims 1, 3, 4, 18, 20, 22, and 24-28 are pending in this application.

Claims 1, 3, 4, 18, 20, 22, and 24-48 as amended are examined on the merits herein.

### Priority

Parent applications 07/438493, 07/487984, 07/115929, and 07/115923, to which priority is claimed, fail to provide adequate written description for any of the instant claims. Specifically, while these parent applications teach various acylated uridine and cytidine derivatives, they do not teach a method of using these derivatives for treating toxicity due to **a pyrimidine nucleoside analog**, much less the specific pyrimidine

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nucleoside analogs recited in the dependent claims. Furthermore they also fail to disclose coadministering these compounds with inhibitors of uridine phosphorylase, cytidine deaminase, or nucleoside transport.

In addition, the parent application 07/724340 fails to provide written description for the subject of claims 1, 3, 4, 18, 20, 22, and 24-28 namely a method of treating toxicity due to an antimalarial agent such as 5-fluoroorotate.

Therefore the effective filing date of the claims 1, 3, 4, 18, 20, 22, and 24-28 is seen to be the filing date of parent application 07/903107, June 25, 1992.

### **Reasons for Allowance**

Applicant's amendment, submitted December 4, 2009, with respect to the rejection of instant claims 1, 18, 20, 22, 24, and 25 under 35 USC 112, first paragraph, for lacking enablement for treating all possible toxicities of pyrimidine analogs, has been fully considered and found to be persuasive to remove the rejection as the claims have been amended to specifically claim a method wherein the toxicity is damage to hematopoietic or mucosal tissue. Therefore the rejection is withdrawn.

Currently claims 1, 3, 4, 18, 20, 22, and 24-28 are pending in this application and have been examined on the merits herein. Applicant's amendment submitted December 4, 2009, and the enclosed examiner's amendment, are seen to be persuasive to remove all rejections of record in the previous office action and place the application in condition for allowance. Reasons for allowance are as follows:

The claimed invention is seen to be adequately described and enabled by the specification as originally filed. Therefore the claims meet the requirements of 35 USC 112.

Furthermore the claims are novel and non-obvious over the prior art. The prior art does not disclose a method using triacetyluridine, ethoxycarbonyluridine, or triacetylcytidine to treat toxicity of a pyrimidine nucleoside. Specifically, the prior art does not disclose these pyrimidine prodrugs as therapeutic compounds. While Davidson et al. (Reference included with PTO-892) discloses an antitumor effect for a complex of triacetyluridine and a platinum compound, which could theoretically be used in a combination chemotherapy regimen, this complex is a distinct molecular species from uncomplexed triacetyluridine, so the reference does not anticipate the claims or render them obvious. Furthermore one of ordinary skill in the art would not be motivated to use the uncomplexed triacetyluridine as a therapeutic agent. Furthermore, the reference Takai et al. (JP-S60-126221, of record in previous action) discloses a combination of 5-fluoro-2'-deoxyuridine and an acylated thymidine compound. However, it would not be obvious to substitute acylated uridine for acylated thymidine in this composition as thymidine and uridine are different compounds that have different roles *in vivo*, as discussed in Applicant's arguments submitted September 29, 2008. As a result the biological effect of an acylated uridine could not be predicted based on a prior art disclosure of acylated thymidine. Therefore the claims meet the requirements of 35 USC 102 and 103.

The parent application 08/176485, now issued as US patent 5736531, was subject to a requirement for restriction between methods of treating cancer, methods of treating pyrimidine nucleoside toxicity, and compositions comprising an acetylated pyrimidine and a chemotherapeutic agent. In the parent application the Applicant elected to pursue the composition claims. As the requirement for restriction was not withdrawn in said application, the present claims are not subject to double patenting rejections against US5736531, or against other commonly owned US patents and applications claiming pharmaceutical compositions or methods of treating cancer, for example US patents 6344447 and 5968914.

Accordingly, Applicant's amendment submitted December 4, 2009, and the attached examiner's amendment, are sufficient to remove all rejections made in the prior office action as discussed above and to place the application in condition for allowance.

Any comments considered necessary by Applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled, "Comments on Statement of Reasons for Allowance."

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eric S. Olson whose telephone number is 571-272-9051. The examiner can normally be reached on Monday-Friday, 8:30-5:00.

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Anna Jiang can be reached on (571)272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Eric S Olson/  
Examiner, Art Unit 1623  
3/3/2010